PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 October 2000 (30.10.00)	
International application No. PCT/EP00/01046	**Applicant's or agent's file reference** 192971001/BN
International filing date (day/month/year) 09 February 2000 (09.02.00)	**Priority date** (day/month/year) 12 February 1999 (12.02.99)
Applicant SCHRÖDER, Ulf et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 September 2000 (06.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Athina Nickitas-Etienne

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

NILSSON, Brita
AB Stockholms Patentbyrå, Zacco & Bruhn
Box 23101
S-104 35 Stockholm
SUÈDE

Date of mailing (day/month/year) 10 April 2001 (10.04.01)	
Applicant's or agent's file reference 192971001/BN	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/01046	**International filing date** (day/month/year) 09 February 2000 (09.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

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Teleprinter No.:

3. Further observations, if necessary:
Please note that the applicant in box 1 has assigned his rights to applicant in box 2.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[X] other: PHARMATRIX AB

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (...)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NILSSON, Brita
Stockholms Patentbyrå Zacco AB
Box 23101
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SUÈDE

Date of mailing (day/month/year) 28 June 2001 (28.06.01)	
Applicant's or agent's file reference 192971001/BN	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/01046	**International filing date** (day/month/year) 09 February 2000 (09.02.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

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Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Athina Nickitas-Etienne Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

6

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
192971001/BN		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01046	09/02/2000	12/02/1999
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant EUROCINE AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/09/2000	04.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moreno de Vega, C Telephone No. +49 89 2399 7486

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01046

I. Basis f th rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-9	as originally filed			

Claims, No.:

1-10	as received on	14/02/2001	with letter of	13/02/2001

Drawings, sheets:

1/2,2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 10.

because:

   ☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and xplanations supporting such stat ment

1. Statement

   Novelty (N) Yes: Claims 1-10

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statem nt

Reference is made to the following documents:

D1: WO 94 17827 A (LYFJATHROUN H F) 18 August 1994 (1994-08-18)
D2: WO 97 47320 A (PHARMATRIX AB) 18 December 1997 (1997-12-18)

The amendments filed with the letter dated 13.02.2001 meet the requirements of Article 34(2)(b) PCT.

This International Preliminary Examining Authority has considered the Applicant's arguments in response to the Written Opinion, and is of the opinion that:

1. Novelty (Article 33(2) PCT)

The subject-matter of claims 1-10 appears to be novel, as it has not been anticipated in the prior art.
D1 (see page 3 line 9 - page 4 line 9, page 9 line 14 - page 10 line 17) discloses pharmaceutical preparations for the topical administration of antigens and/or vaccines to mammals via mucosal membranes using adjuvants as claimed in present claims 1 and 5 (oleic acid, soybean oil) in a mixture with others excipients, said preparation being used for the preparation of vaccines, i.e. tuberculosis. D1 does not disclose the use of a combination of a monoglyceride and a fatty acid as adjuvant in a vaccine

composition.

2. Inventive step (Article 33(3) PCT)

D2 (see page 4 line 15 - page 5 line 31 and claims) discloses a pharmaceutical formulation for parenteral or mucosal administration of antigens or vaccines comprising monoglyceride preparations having at least 80% monoglyceride content and where the acyl group contains from 6 to 24 carbon atoms, together with fatty acids where the number of carbon atoms may be varied between 4 and 22.

The present application differs from D2, which is considered to be the most relevant prior art, in the use of the described adjuvant in the formulation of a TB vaccine. The technical problem to be solved by the present invention is the provision of improved TB vaccine compositions. The teaching of the known prior art does not provide neither hint to use the adjuvants of D2 in the formulation of a TB vaccine nor the success of this vaccine.

Thus, claims 1-10 do meet the requirements of Article 33(3) PCT.

3. For the assessment of the present claim 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

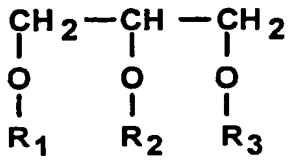
192971001/BN

Claims

1. Tuberculosis (TB) vaccine composition comprising,

as adjuvant, one or more substances selected from

a) monoglyceride preparations having at least 80 % monoglyceride content and having the general formula



wherein R_1 and R_2 is H and R_3 is one acyl group containing from 6 to 24 carbon atoms, and where the acyl chains may contain one or more unsaturated bonds, together with one or more substances selected from

b) fatty acids of the general formula

$$CH_3 - (CH_2)_n - COOH$$

where "n" may be varied between 4 and 22, and where the acyl chain may contain one or more unsaturated bonds, and

as immunizing component, inactivated *Mycobacterium tuberculosis* bacteria.

2. TB vaccine composition according to claim 1, wherein the *M. tuberculosis* bacteria are heat killed or formalin killed.

3. TB vaccine composition according to claim 1 or 2, wherein the adjuvant has a monoglyceride preparation content of at least 90 %, preferably at least 95 %, and the acyl chains of the monoglyceride preparation contains 8 to 20 carbon atoms, preferably 14 to 20 carbon atoms, and the acyl chains optionally contains one or more unsaturated bonds.

4. TB vaccine composition according to any one of claims 1 - 3, which further comprises pharmaceutical excipients selected from the group consisting of biocompatible oils, physiological saline solution, preservatives and osmotic pressure controlling agents, carrier gases, pH-controlling agents, organic solvents, hydrophobic agents, enzyme inhibitors, water absorbing polymers, surfactants, absorption promoters, and anti-oxidative agents.

5. TB vaccine composition according to claim 3 or 4, wherein the adjuvant is a mixture of mono-olein and oleic acid, and possibly soybean oil, and the immunizing component is heat-killed *M. tuberculosis* bacteria.

6. TB vaccine composition according to any one of claims 1-5, wherein the composition is formulated into a preparation for mucosal administration.

7. TB vaccine composition according to claim 6, wherein the mucosal administration is selected from nasal, pulmonary, oral and vaginal administration.

8. Aerosol or spray package comprising a TB vaccine composition according to any one of the claims 1 - 7.

9. Nose-drop package comprising a TB vaccine composition according to any one of the claims 1 - 7.

10. A method of vaccinating a mammal against Tuberculosis (TB) which comprises mucosal administration to the mammal of an protection-inducing amount of a TB vaccine composition according to any one of claims 1 - 7.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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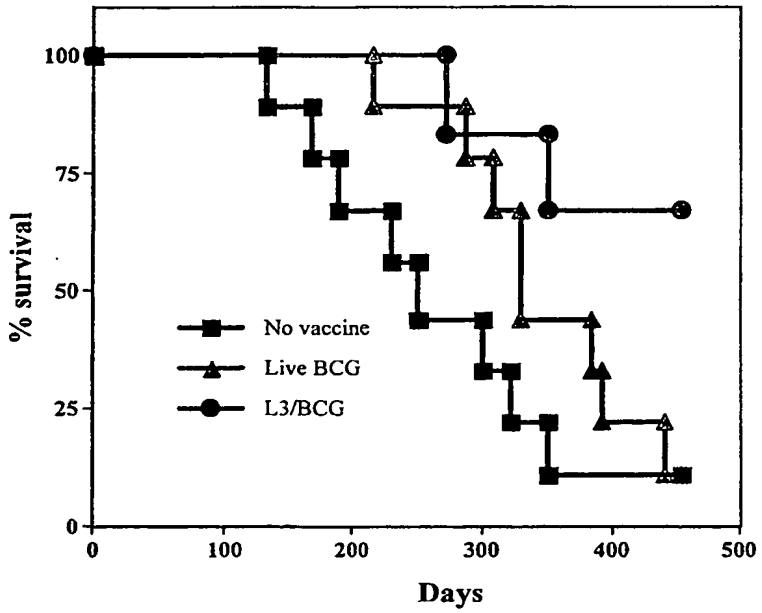
(54) Title: VACCINE COMPOSITION



(57) Abstract

A tuberculosis (TB) vaccine composition is disclosed. The composition comprises, as adjuvant, one or more substances selected from a) monoglyceride preparations having at least 80% monoglyceride content and b) fatty acids of the general formula $CH_3 - (CH_2)_n - COOH$ where "n" may be varied between 4 and 22, and where the acyl chain may contain one or more unsaturated bonds, and as immunizing component, inactivated, e.g. heat killed or formalin killed, *Mycobacterium tuberculosis* bacteria.

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VACCINE COMPOSITION

The present invention relates to a novel tuberculosis (TB) vaccine composition. The preferred route of administration is via the mucosal membranes.

BACKGROUND

The earliest described immunization attempts were carried out in China over 900 years ago, where intranasal inoculation of dried and ground smallpox pustules was performed. In the classical immunology and in combination with vaccination against different types of infectious agents e.g. bacteria, virus or parasites the prevailing dogma has been to administer the vaccine subcutaneously or intramuscularly. However, research has during the last years shown that the body has a very effective immunological system that resides in the mucosa. It has also been shown that you can administer vaccines nasally, orally, rectally and vaginally. In the same way as for the classical immunization it has been shown that by mucosal vaccination there is also a need for enhancement of the immunological response by the addition of adjuvants.

The intranasal route has attracted increased attention because of the greater efficacy in inducing mucosal immune responses than the more conventional regimes of parenteral immunization. Furthermore, the realization that approximately 80% of the immune system reside in the mucosa combined with the fact that an equal percentage of the known pathogens enter our bodies via the mucosal membranes has pushed the interest towards the application of mucosal immunization.

It has also been shown that parenteral vaccines do not induce immune response at mucosal sites. Thus, it is also clear that appropriate stimulation of a mucosal site such as the nose or the gut, can generate immune response at other mucosal sites. As an example, it is possible to apply a vaccine in the nose and obtain an immune response in the vagina. Furthermore, the mucosal immune response is very rapid with onset only hours after being subjected to stimulation by a pathogen, as compared to parenteral immunity having a response time of several days.

Tuberculosis (TB) is one of the major causes of morbidity in the world with an estimated death toll of approximately 3 millions per year. It is estimated that 1/3 of the world's population is infected with TB. To a large extent TB is essentially an

uncontrolled problem despite the use of the Bacille Calmette-Guérin (BCG) vaccine for more than 75 years.

The BCG vaccine consists of a weakened strain of tuberculosis bacteria taken from a cow in 1908. The original bacteria used today were cultured for 13 years for the purpose of weaken their pathogenic characteristics in order to be used as live bacteria for parenteral vaccination of humans. Basically the same strain is used today as the only vaccine available against TB. Several pharmaceutical companies around the world produce the BCG vaccine. The BCG formulation used today consists of freeze-dried attenuated viable BCG vaccine in one container and another container with physiologically acceptable suspension media. Before administration, the freeze-dried BCG is suspended and subsequently administered by injection to the patient. This procedure which has to be carried out immediately in connection with the vaccination, requires skilled personnel and decent facilities in order to avoid contamination. Unfortunately these criteria are hard to keep up with in the developing countries. Thus, it is estimated that failure to keep to this standard costs about USD 500 millions each year world wide. Consequently, huge savings could be made both in money and product safety, if a system was available where no mixing of vaccines was needed and where injections could be eliminated, thus eliminating the need for highly skilled personnel and sterile conditions.

In clinical trails around the world, the protective efficacy of the BCG vaccine has been shown to vary between -50% to +80%. This means that certain clinical studies have shown that in fact you enhance instead of diminish your risk of getting the disease after vaccination.

The BCG vaccine works well for children but has more or less no effect on adults. Consequently there are great efforts made in order to achieve a vaccine against TB for the grown-up population. Up to date however, there are no reports in the literature of a TB vaccine that is better than BCG.

Tuberculosis is spread by close person-to-person contact through infectious aerosols. On rare occasions the disease can be acquired by ingestion or skin trauma. This means that the first organ to get into contact with the bacteria during a normal infection is the mucosal surfaces in the lungs.

Adjuvants are a heterogeneous group of substances that enhance the immunological response against an antigen that is administered simultaneously.

Almost all adjuvants used today for enhancement of the immune response against antigens are particles or are forming particles together with the antigen. In the book "Vaccine Design - the subunit and adjuvant approach" (Ed: Powell & Newman, Plenum Press, 1995) almost all known adjuvants are described both regarding their immunological activity and regarding their chemical characteristics. As described in the book more than 80% of the adjuvants tested today are particles or polymers that together with the antigens (in most cases proteins) are forming particles. The type of adjuvants that are not forming particles are a group of substances that are acting as immunological signal substances and that under normal conditions consist of the substances that are formed by the immune system as a consequence of the immunological activation after administration of particulate adjuvant systems.

Using particulate systems as adjuvants, the antigens are associated or mixed with or to a matrix, which has the characteristics of being slowly biodegradable. Of great importance using such matrix systems are that the matrices do not form toxic metabolites. Choosing from this point of view, the main kinds of matrices that can be used are mainly substances originating from a body. With this background there are only a few systems available that fulfill these demands: lactic acid polymers, poly-amino acids (proteins), carbohydrates, lipids and biocompatible polymers with low toxicity. Combinations of these groups of substances originating from a body or combinations of substances originating from a body and biocompatible polymers can also be used. Lipids are the preferred substances since they display structures that make them biodegradable as well as the fact that they are the most important part in all biological membranes.

Lipids are characterized as polar or non-polar. The lipids that are of most importance in the present invention are the polar lipids since they have the capacity to interact and form particulate systems in water. Another way of defining these lipids are as amphiphilic due to their chemical structure with one hydrophobic and one hydrophilic part in the molecule thereby being useable as surface active substances. Examples of main groups of polar lipids are mono-glycerides, fatty acids, phospholipids and glycosphingolipids. These main groups can be further characterized depending on the length of the acyl chain and the degree of saturation of the acyl chain. Since the number of carbon atoms in the acyl chain can be in the range of 6 to 24, and the number of unsaturated bonds can be varied, there is an almost infinite number of combinations regarding the chemical composition of the lipid.

Particulate lipid systems can be further divided into the different groups as discussed in the scientific literature such as liposomes, emulsions, cubosomes, cochleates, micelles and the like.

In a number of systems the lipids may spontaneously form, or can be forced to form, stabile systems. However, under certain circumstances other surface-active substances have to be introduced in order to achieve stability. Such surface-active systems can be of non-lipid character but possess the characteristics of the polar lipids having hydrophobic and hydrophilic parts in their molecular structure.

Another factor that has been shown to be of importance is that lipids exhibit different physical chemical phases, these phases have in different test systems been shown to enhance uptake of biological substances after administration to mucous membranes. Examples of such physical chemical phases described are L2, lamellar, hexagonal, cubic and L3.

In the same way as within the classical immunology where vaccines (antigens) are administered parenterally, there is within mucosal immunization a great interest in directing the immunological response towards development of humoral and/or cellular response. If you obtain a humoral response it would be important to direct the response in a way that a certain class of antibodies would be obtained. In order to obtain such a goal, specific immune stimulating agents can be added to the formulation of antigens and adjuvants.

A formulation which fulfils these goals is described in PCT/SE97/01003, the contents of which is incorporated herein by reference. The disclosed formulation comprises monoglycerides and fatty acids. The monoglycerides comprise one or more substances selected from monoglycerides wherein the acyl group contains from 6 to 24 carbon atoms, preferably 8 to 20 carbon atoms, even more preferably 14 - 20 carbon atoms and where the acyl chain may contain unsaturated bonds.

The acyl chain of the fatty acid may be varied between 4 and 22, preferably 8 to 18 and where the acyl chain may contain one or more unsaturated bonds. A combination of the monoglyceride mono-olein and oleic acid has shown to be an L3 phase, which can be described as sponge-like structure, in contrast to liposomes that form onion-like lamellar structures.

Said combination of monoglycerides and fatty acids my be further formulated by the addition of a biocompatible and biodegradable oil thus forming an oil in water

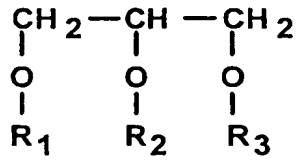
(o/w) or w/o/w emulsion. Such emulsions have been shown in the literature to be very effective in enhancing the cellular response against an antigen after administration to an animal (Singh, M., et al 1997, *Vaccine* 15, 1773-78). It is generally accepted that in order to have an acceptable vaccine against TB there is a need for a cellular immune response.

Description of the invention

The present invention is directed to a tuberculosis (TB) vaccine composition comprising,

as adjuvant, one or more substances selected from

a) monoglyceride preparations having at least 80 % monoglyceride content and having the general formula



wherein R_1 and R_2 is H and R_3 is one acyl group containing from 6 to 24 carbon atoms, and where the acyl chains may contain one or more unsaturated bonds and

b) fatty acids of the general formula

$$CH_3 - (CH_2)_n - COOH$$

where "n" may be varied between 4 and 22, and where the acyl chain may contain one or more unsaturated bonds, and

as immunizing component, inactivated *Mycobacterium tuberculosis* bacteria. In a preferred embodiment the *M. tuberculosis* bacteria are heat killed or formalin killed.

The adjuvant of the vaccine composition of the invention preferably has a monoglyceride preparation content of at least 90 %, preferably at least 95 %, and the acyl chains of the monoglyceride preparation contains 8 to 20 carbon atoms, preferably 14 to 20 carbon atoms, and the acyl chains optionally contains one or more unsaturated bonds.

The TB vaccine composition according to the invention may further comprise pharmaceutical excipients selected from the group consisting of biocompatible oils, such as rape seed oil, sunflower oil, peanut oil, cotton seed oil, jojoba oil, squalan or squalene, physiological saline solution, preservatives and osmotic pressure controlling

agents, carrier gases, pH-controlling agents, organic solvents, hydrophobic agents, enzyme inhibitors, water absorbing polymers, surfactants, absorption promoters, and anti-oxidative agents.

In a most preferred embodiment of the invention the TB vaccine composition comprises, as adjuvant, a mixture of mono-olein and oleic acid, and possibly soybean oil, and, as immunizing component, heat-killed *M. tuberculosis* bacteria.

In a preferred embodiment the TB vaccine composition of the invention is formulated into a preparation for mucosal administration, such as nasal, pulmonary, oral or vaginal administration.

Another aspect of the invention is directed to an aerosol or spray package comprising a TB vaccine composition according to the invention.

A further aspect of the invention is directed to a nose-drop package comprising a TB vaccine composition according to the invention.

Yet another aspect of the invention is directed to method of vaccinating a mammal against Tuberculosis (TB) which comprises mucosal administration to the mammal of a protection-inducing amount of a TB vaccine composition according to the invention.

As described above the present commercially available vaccine against TB comprises of an attenuated strain of the bacteria. Such systems may under certain circumstances, when administered as a vaccine, result in an infection by the attenuated bacteria. Thus, attenuated systems are preferentially used when killed organisms are unable to give protective immunity. Thus, the preferred system is an inactivated organism or a purified antigen from the pathogen, which, in combination with adequate adjuvants results in protective immunity. Furthermore, inactivated pathogens are more stable and consequently more attractive as antigens/vaccines, especially in the developing world. Such inactivation may be performed by heat or by treatment with formalin, both of which is well established and well known to the man skilled in the art.

The TB vaccine composition according to the invention may be prefabricated, and no need for skilled personnel is needed upon nasal administration, thereby eliminating injection systems such as needles and syringes which in developing world often are contaminated and thus are spreading diseases between patients. Furthermore, a device for multidose aerosol delivery of a nasal vaccine can easily be constructed in way that no person-to-person infection can occur.

The invention will now be illustrated by way of an example, which, however, is not to be interpreted as limitation to the scope of protection according to the appended claims.

Short description of the drawings

Fig. 1 shows the results of the testing disclosed in Example 1.

Fig.2 shows the survival rate for the same mice as described in Fig 1.

EXAMPLE 1 (BCG)

Protection of C57BL mice from intranasal sub-lethal challenge with *M. tuberculosis* (MT) by immunization with live BCG and heat-killed BCG in two different L3 lipid adjuvant formulations.

Emulsion; one ampoule of freeze-dried BCG bacteria was suspended in the suspension media as supplied by the manufacturer (Statens Seruminstitute, Denmark) and heat-killed at +60°C for 10 minutes. The emulsion was produced by mixing the heat-killed BCG suspension with 200 µl of soybean oil and 110 µl of a mixture of mono-olein and oleic acid (1:1). This mixture was sonicated briefly for a few seconds whereupon 3.2 ml of 0.1 M TRIS buffer and 40 µl of 4 M NaOH were added. Sonication was performed for 2 minutes whereupon the emulsion was used for immunization.

An L3 suspension is produced from a 1:1 molar mixture of mono-olein and oleic acid (1.43 g of mono-olein and 1.12 g of oleic acid) which was added to 20 ml of 0.1 M Triss buffer. Prior to sonication for 2 minutes, 640 µl of 4 M NaOH are added. Before immunization the L3 adjuvant is mixed at a 1:1 ratio with the heat-killed BCG.

Adjustments of the amount of suspension media were made so that each mouse received the same amount of BCG bacteria whether given parenterally or nasally.

Immunization 1; 0 weeks (parenteral for all groups). Immunization 2; 3 weeks (nasally for all groups except live BCG which was administered parenterally). Challenge; 4 weeks.

Changes of body weight (%) related to initial weight at time 0 weeks.

Average body weight changes ± SE are shown in Fig.1.

As can be seen from the weight changes both of the adjuvant formulations containing heat-killed BCG result in a positive body-weight development as compared to non-adjuvanted BCG (alive or killed).

In Fig.2 is seen the survival rate for the same mice as described in Fig 1. As can be seen approximately 70% of the mice receiving heat-killed BCG formulated with the lipid adjuvant according to the present invention were still alive when the experiment was terminated. In contrast, in the groups receiving classical live BCG or no vaccine at all, only approximately 10 of the mice were alive when the experiment was terminated.

EXAMPLE 2

Mice (female) were immunised on day 0 and after 3 weeks with different vaccine formulations whereupon the mice were killed after 11 weeks. The spleens of the mice were taken out and the lymphocytes were purified and subsequently subjected to immunological assays in order to establish the efficacy of the formulations to induce immunologically active lymphocytes.

In the following example, the lymphocytes were stimulated with an extract from *M. tuberculosis*. Simultaneously ^{3}H-labelled thymidine was added to the cells. As the immunologically activated cells proliferate, the ^{3}H-labelled thymidine is incorporated into the genomes of the proliferating cells. Next, the ^{3}H-labelled thymidine was measured. A high uptake of labelled thymidine indicates the strength of the lymphocyte immune response.

The following vaccine formulations were tested:

BCG: Live standard BCG vaccine (Statens Seruminstitute, Denmark) injected into three mice on day 0.

BCG/L3: Live standard BCG vaccine (Statens Seruminstitute, Denmark) was used as primary vaccination and subsequently the mice were vaccinated intra- nasally with a heat-killed BCG/ L3 vaccine, (according to Example 1) as a booster-vaccination on day 21.

L3/L3: On day 0 the mice were injected with the heat-killed BCG/L3 formulation according to Example 1, followed by a nasally administered booster - vaccination after 3 weeks using the same formulation.

The results are presented in Table 1.

TABLE 1	Formulation	^{3}H-thymidine uptake (cpm)
	BCG	2153
	BCG/L3	1337
	L3/L3	4583

The results indicate that the formulation according to the present invention is superior in stimulating lymphocytes as compared to standard BCG vaccination with live BCG.

EXAMPLE 3

Another set of mice was subjected to the same vaccination procedures and formulations as described in Example 2 above. However, 8 weeks after the booster immunization the mice were challenged with a *M. tuberculosis* -containing aerosol. Another 4 weeks later the mice were killed and the lymphocytes from the spleens were collected. The lymphocytes were allowed to grow for five days whereupon the amounts

of Tumor Necrosis Factor Alfa (TNF-α) were determined in cell-supernatants. Elicitation of low levels of TNF-α is a desired property of any new vaccine candidate against tuberculosis because of its well-documented noxious side effects and hence, any candidate vaccine that can prevent TNF-α production upon infection would be regarded as superior.

Table 2. Concentrations of TNF-α as compared to a group of mice that has been challenged on week 11 with *M. tuberculosis* without prior immunization.

TABLE 2	Formulation	TNF-α (pg)
	BCG	43
	BCG/L3	18
	L3/L3	9
	Challenge only	60

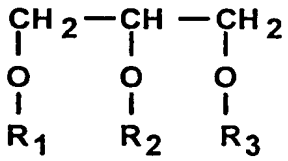
As can be seen from Table 2, the present invention using heat killed BCG together with an emulsion according to the present invention results in the lowest level of TNF-α

Claims

1. Tuberculosis (TB) vaccine composition comprising,

as adjuvant, one or more substances selected from

a) monoglyceride preparations having at least 80 % monoglyceride content and having the general formula



wherein R_1 and R_2 is H and R_3 is one acyl group containing from 6 to 24 carbon atoms, and where the acyl chains may contain one or more unsaturated bonds and

b) fatty acids of the general formula

$$CH_3 - (CH_2)_n - COOH$$

where "n" may be varied between 4 and 22, and where the acyl chain may contain one or more unsaturated bonds, and

as immunizing component, inactivated *Mycobacterium tuberculosis* bacteria.

2. TB vaccine composition according to claim 1, wherein the *M. tuberculosis* bacteria are heat killed or formalin killed.

3. TB vaccine composition according to claim 1 or 2, wherein the adjuvant has a monoglyceride preparation content of at least 90 %, preferably at least 95 %, and the acyl chains of the monoglyceride preparation contains 8 to 20 carbon atoms, preferably 14 to 20 carbon atoms, and the acyl chains optionally contains one or more unsaturated bonds.

4. TB vaccine composition according to any one of claims 1 - 3, which further comprises pharmaceutical excipients selected from the group consisting of biocompatible oils, physiological saline solution, preservatives and osmotic pressure controlling agents, carrier gases, pH-controlling agents, organic solvents, hydrophobic agents, enzyme inhibitors, water absorbing polymers, surfactants, absorption promoters, and anti-oxidative agents.

5. TB vaccine composition according to claim 3 or 4, wherein the adjuvant is a mixture of mono-olein and oleic acid, and possibly soybean oil, and the immunizing component is heat-killed *M. tuberculosis* bacteria.

6. TB vaccine composition according to any one of claims 1-5, wherein the composition is formulated into a preparation for mucosal administration.

7. TB vaccine composition according to claim 6, wherein the mucosal administration is selected from nasal, pulmonary, oral and vaginal administration.

8. Aerosol or spray package comprising a TB vaccine composition according to any one of the claims 1 - 7.

9. Nose-drop package comprising a TB vaccine composition according to any one of the claims 1 - 7.

10. A method of vaccinating a mammal against Tuberculosis (TB) which comprises mucosal administration to the mammal of an protection-inducing amount of a TB vaccine composition according to any one of claims 1 - 7.

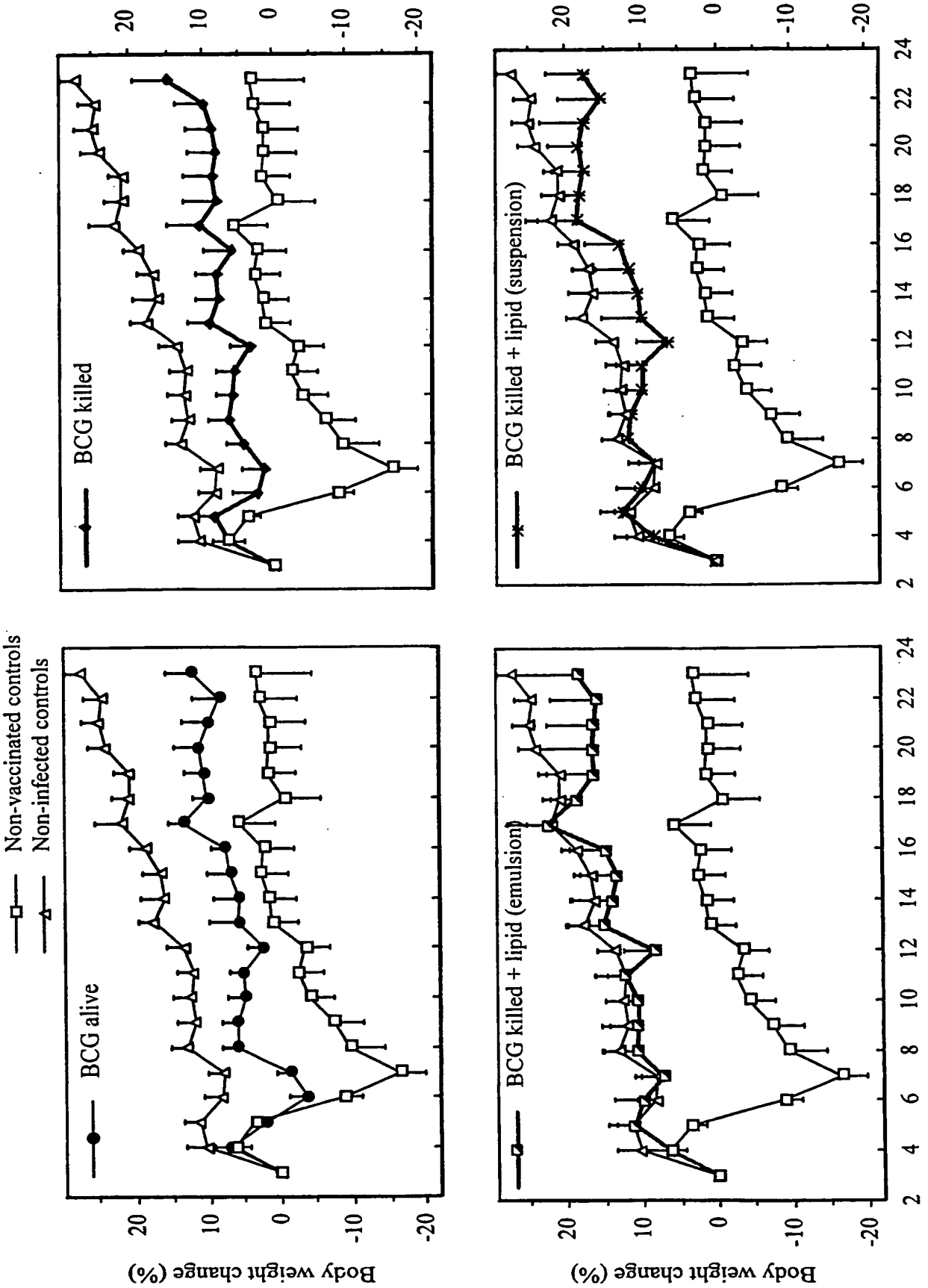

Non-vaccinated controls
Non-infected controls
BCG alive
BCG killed
BCG killed + lipid (emulsion)
BCG killed + lipid (suspension)
Body weight change (%)
Body weight change (%)
20
10
0
-10
-20
2
4
6
8
10
12
14
16
18
20
22
24

Fig. 1

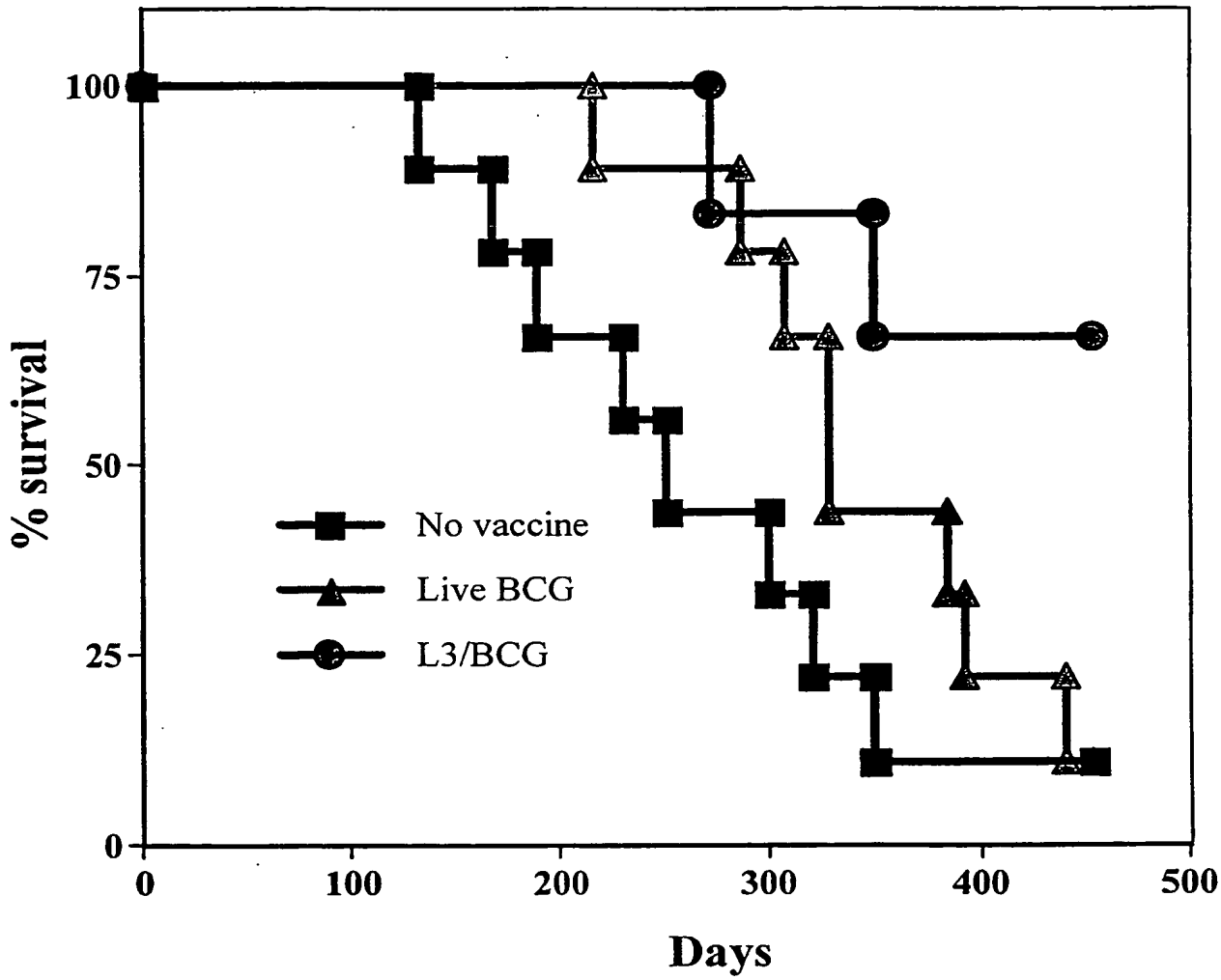

100
75
50
25
0
% survival
No vaccine
Live BCG
L3/BCG
0
100
200
300
400
500
Days

Fig. 2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WO 00/47225 A3

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(25) Filing Language: English

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(30) Priority Data:
9900495-4 12 February 1999 (12.02.1999) SE

(71) Applicant *(for all designated States except US)*: **PHARMATRIX AB** [SE/SE]; Spelmanshöjden 14, S-174 50 Sundbyberg (SE).

(72) Inventors; and
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(74) Agents: **NILSSON, Brita** et al.; AB Stockholms Patentbyrå, Zacco & Bruhn, Box 23101, S-104 35 Stockholm (SE).

(81) Designated States *(national)*: AU, CA, JP, NZ, US.

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Published:
— *With international search report.*

(88) Date of publication of the international search report:
14 December 2000

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/47225 A3

(54) Title: TUBERCULOSIS VACCINE FORMULATION COMPRISING MONOGLYCERIDES OR FATTY ACIDS AS ADJUVANT

(57) Abstract: A tuberculosis (TB) vaccine composition is disclosed. The composition comprises, as adjuvant, one or more substances selected from a) monoglyceride preparations having at least 80% monoglyceride content and b) fatty acids of the general formula CH_3 - $(CH_2)_n$ - COOH where "n" may be varied between 4 and 22, and where the acyl chain may contain one or more unsaturated bonds, and as immunizing component, inactivated, e.g. heat killed or formalin killed, *Mycobacterium tuberculosis* bacteria.

INTERNATIONAL SEARCH REPORT

Inte[redacted]onal Application No
P[redacted]EP 00/01046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 17827 A (LYFJATHROUN H F) 18 August 1994 (1994-08-18) abstract page 4, line 1 - line 8 page 9, line 14 -page 10, line 17 ---	1-10
Y	WO 97 47320 A (PHARMATRIX AB) 18 December 1997 (1997-12-18) abstract page 4, line 15 -page 5, line 31 page 7, line 6 - line 9 ---	1-10
A	WO 93 06921 A (GS BIOCHEM AB) 15 April 1993 (1993-04-15) page 8, line 34 -page 9, line 2 page 37, line 17 - line 20 page 38, line 17 - line 23 page 45, line 1 -page 47, line 8 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000	08. 08. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	C-O Gustafsson/Eö

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte[redacted]ional Application No
P[redacted]EP 00/01046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	SCHRÖDER U ET AL: "Nasal and parenteral immunizations with diphteria toxoid using monoglyceride/fatty acid lipid suspensions as adjuvants" VACCINE, vol. 17, 1999, pages 2096-2103, XP002901071 the whole document -----	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP00/01046

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP000/01046

Claim 10 relates to a method of treatment of the human or animal b dy by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL [redacted]RCH REPORT

Informati n on patent family members

02/12/99

International application No.
PCT/EP 00/01046

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417827 A1	18/08/94	AU 668290 B	26/04/96
		AU 6106594 A	29/08/94
		CA 2156084 A	18/08/94
		EP 0682528 A	22/11/95
		JP 9508614 T	02/09/97
		NO 953182 A	12/10/95
		US 5942237 A	24/08/99
WO 9747320 A1	18/12/97	AU 3199897 A	07/01/98
		CA 2258017 A	18/12/97
		EP 0918541 A	02/06/99
		SE 9602280 D	00/00/00
WO 9306921 A1	15/04/93	AT 182278 T	15/08/99
		AU 2699892 A	03/05/93
		BR 9206593 A	28/11/95
		CA 2120359 A	15/04/93
		DE 69229640 D	00/00/00
		EP 0643620 A,B	22/03/95
		ES 2133391 T	16/09/99
		FI 941538 A	31/05/94
		JP 7502197 T	09/03/95
		NO 941191 A	01/06/94
		US 5531925 A	02/07/96

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
192971001/BN		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/01046	09/02/2000	12/02/1999
Applicant		
PHARMATRIX AB et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   TUBERCULOSIS VACCINE FORMULATION COMPRISING MONOGLYCERIDES OR FATTY ACIDS AS ADJUVANT

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL-TYPE SEARCH REPORT

Search request No.
SE 99/00166

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 39/39
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9417827 A1 (LYFJATHROUN H.F.), 18 August 1994 (18.08.94), see abstract; page 4, lines 1-8; page 9, line 14 - page 10, line 17 --	1-10
Y	WO 9747320 A1 (PHARMATRIX AB), 18 December 1997 (18.12.97), see abstract; page 4, line 15 - page 5, line 31; page 7, lines 6-9 --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international-type search	Date of mailing of the international-tupe search report
3 September 1999	1999 -09- 06
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Patrick Andersson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL-TYPE SEARCH REPORT

Search request No.
SE 99/00166

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9306921 A1 (GS BIOCHEM AB), 15 April 1993 (15.04.93), see page 8, line 34 - page 9, line 2; page 37, lines 17-20; page 38, lines 17-23; page 45, line 1 - page 47, line 8	1-10

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